REMARKS

In this Amendment, claims 1-106 have been canceled without prejudice or disclaimer. New claims 107-153 have been added to place the claims in condition for allowance or in better form for appeal. Of the newly presented claims, claim 108 is similar to former claim 96; claim 109 is similar to former claim 100; claim 110 is similar to former claim 101; claim 113 is similar to former claim 106; and claim 115 is similar to former claim 3.

Claims 4-16, 28-44, 56-83, 85-91 and 97-99, withdrawn as directed to a non-elected invention, are cancelled without prejudice or disclaimer to provide a complete response to the Office Action. Applicants preserve the right to timely file one or more divisional applications covering the non-elected subject matter.

No new matter has been added by virtue of the new claims, which are supported by the claims and the application as originally filed. Specifically, support for the recitation that the methods of claims 116 and 130 augment or bulk tissue mass is found in the instant specification, *inter alia*, on page 7, line 3. Support for new claims 125-130 is found in the instant specification, *inter alia*, on page 17, lines 14-20; and on page 20, line 20 to page 21, lines 1-27. Support for claims 130, 137 and 147 is found in the instant specification, *inter alia*, on pages 32-33, Example 4 and in Fig. 2; and on pages 40-42, 44, 45 and 48-50, Example 9 and in Fig. 15, for example. Claims 107-153 are currently pending in this application.

Drawings

Applicants have included a petition filed under 37 C.F.R. §1.84(b)(2) for use of the figures filed in color in the instant application as acceptable drawings (photographs). In addition to the petition, applicants further provide the requisite fee (to be charged to the Deposit Account), copies of the color figures in triplicate and an amendment to the first paragraph of the brief description of the figures, as required for acceptance of the figures in color and as provided hereinabove.

The claims fulfill the requirement of 35 U.S.C. §112, first paragraph

Claims 1, 3, 17-26, 45-54, 84, 92, 93, 96 and 100-106 stand rejected under 35 U.S.C. §112, first paragraph. According to the Examiner, the listed claims contain subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

Applicants respectfully disagree with this rejection and submit that the claims as presented herein satisfy the requirements of §112, first paragraph. However, without acquiescing to the propriety of this rejection, applicants cancel without prejudice claim 1 and 96 and submit that this obviates the specific rejection of these claims under §112, first paragraph.

The presently claimed invention is directed to a method of obtaining muscle derived progenitor cells (MDC), involving plating and culturing muscle cells, preferably of mammalian origin, e.g., fetal and adult mice, rats, pigs, rabbits and humans. The instant application teaches that MDCs are obtainable from any mammal having a muscle source, e.g., smooth muscle or skeletal muscle. Once the muscle cells are obtained, they are subjected to the plating and culturing protocol until an end population of MDCs is attained, as described in the instant specification. Accordingly, the practice of applicants' claimed method of MDC isolation results in obtaining MDCs that comprise the compositions used in methods of bulking and augmenting muscle tissue mass and treating tissue weakness and dysfunction, as claimed herein.

The presently claimed invention complies with §112, first paragraph, by describing the means of attaining the isolated MDCs. (See, e.g., Example 1, page 28, lines 30-31 to page 29, lines 1-28). Accordingly, the Examiner's concerns (03/11/03 Office Action, p. 6) have been addressed. Practice of the presently claimed method of obtaining MDCs as taught in the instant specification allows the skilled practitioner to isolate the MDCs without undue experimentation. In addition, the skilled person in the art can then utilize the MDCs obtained by the presently claimed MDC isolating method

without undue experimentation. There is no *a priori* reason to believe that one having skill in the art cannot isolate MDCs from muscle tissue according to the method taught and described by the applicants by other than routine skill. The isolated MDCs can then be employed alone or in compositions in the described methods of augmenting and bulking tissue and for ameliorating or repairing tissue weakness and dysfunction. Applicants submit that the presently claimed method of isolating MDCs and the MDCs obtained therefrom allow one having skill in the art to make and use the invention without any undue or excessive experimentation. Moreover, the method can be performed using a muscle cell source from a mammal, thereby providing an obtainable MDC end cell population that is readily envisioned by one skilled in the art.

Applicants have disclosed, and the previously submitted declaration of Dr. Chancellor has stated, that MDCs can be obtained from smooth or skeletal muscle preparations of a variety of mammalian species. In view of the teachings of the application and the description of the method in the specification, no undue experimentation is involved in obtaining a starting population of muscle cells from a mammalian source, and carrying out the claimed method of MDC isolation. Such MDCs as obtained from the claimed isolation method can be used in the claimed methods of bulking and augmenting tissue and in treating tissue weakness and dysfunction. The previously-submitted declaration of Dr. Michael Chancellor describes the use of the presently claimed MDC in the disclosed treatments in art-accepted animal models, such as mice. (See, e.g., ¶¶ 9 (a)-9(e) of the Chancellor declaration). The use of MDCs obtained as described in the instant application is further supported by the enclosed declaration of Dr. Tracy Cannon. (¶¶ 4, 8 and 9, for example).

The Examiner has previously recognized (i.e., on page 7, last paragraph to page 8, lines 1-2 of the May 22, 2002 Office Action) that applicants have provided numerous working examples in which the applicability of the isolated MDCs has been demonstrated in more than one *in vivo* system. Both rats and mice show efficacy of treatment using the MDCs obtained by the method of the applicants. (e.g., "Examples 3-5 and 7-8 display that genetically modified MDC with LacZ were viable for up to 4

weeks in the lower abdomen of rats as shown in Example 3 (pages 32-33 and 39-40). Example 6 displays an increase in the contraction amplitude and contraction velocity (i.e., functional characteristics) of bladder strips of cryodamaged bladder tissue in rats using MDC (pages 33-39). Example 9 displays that genetically modified mc13 cells with adBMP-2 can cause bone formation (pages 40-51).

The MDCs as described in the instant application were shown to be able to repopulate an area of the bladder into which they were introduced and restore function to such damaged bladder muscle tissue following introduction or transplantation into the site of the damaged tissue. Indeed, applicants have previously presented publications of the inventors' own work, in collaboration with their technical laboratory researchers, which are cumulative to the instant disclosure and support long term survival of MDCs and resulting myofiber formation in urethral and bladder wall (See, for example, T. Yokoyama et al., 2000, *World J. Urol.*, 18:56-61, Exhibit 2; T. Yokoyama et al., 2001, *J. Urol.*, 165:271-276, Exhibit 3; and J.Y. Lee et al., 2001, *J. Urol.*, 165(5), Supplement, 1033A:251, Exhibit 4, as provided with applicants' 11/21/2002 response).

In addition, experimental work based on the instant application, which was performed after the filing of the instant application and which follows and reproduces the teachings of the application, further demonstrates that MDC isolated from both mice and rats can be used as described in the instant specification. Both mouse and rat hosts have been shown to respond to injection of the isolated MDC by harboring viable muscle cells that function as muscle cells upon later investigation, i.e., over two weeks post injection. For example, the enclosed publication of J.Y. Lee et al. (J.Y. Lee et al., 2003, *Int. Urogynecol. J. Pelvic Floor Dysfunct.*, 14(1):31-37) reports the successful use of rat MDC isolated as described in the instant application as a periurethral bulking agent to increase leak point pressure resulting from sphincter deficiencies in a denervated female rat model of stress urinary incontinence. In this publication, it was found that the rat MDC injected into the denervated urethral sphincter muscle of anesthetized rats caused an increase in dorsolateral skeletal muscle masses with variable fiber orientation at the injection sites after four weeks. It was further shown

that MDC isolated from rats as described by applicants survived in the lower urinary tract, developed into myofibrils to increase the presence of skeletal muscle fibers around the urethra and increased the leak point pressure in denervated rats following periurethral injection. (See, Cannon declaration, ¶ 4). Thus, practice of the claimed invention is supported by published demonstrations of MDC use in augmenting and bulking muscle tissue.

The Examiner refers to particular statements in a publication of Lee et al. (i.e., J.Y. Lee et al., 2000, *J. Cell Biol.*, 150:1085-1099) to support the Examiner's opinion that the art related to cell (e.g., myoblast) transplantation has been hindered by various limitations. (*See,* 03/11/03 Office Action, p. 9). Although the passage related to the teaching of Lee et al. on page 9 of the Office Action appears to be a direct quotation, it is not the identical wording of the publication. In this passage, the Examiner remarks that the Lee et al. publication states that the mechanism by which muscle derived cells display a high cell survival is unclear. However, a mechanism need not be known or understood in order for an invention to be patentable. Thus, this statement in the publication does not reflect adversely on applicants' claimed invention.

Regarding the statements cited by the Examiner from pp. 1096-1097 of the Lee et al. publication, Lee et al. in this passage of the publication discuss the differences between the earlier populations of muscle cells (i.e., cells of the early platings prior to isolating the end population of MDCs in the last plating) and the end cell population that comprises the MDCs, as discovered by the applicants. These statements by Lee et al. also do not specifically address any limitations that would affect applicants' presently claimed invention, since applicants teach in their specification that the MDCs having pluripotency for use in the claimed methods are isolated from the later platings of applicants' claimed MDC isolation method.

The instant disclosure teaches a method of isolating MDCs from the muscle tissue of mammals, as exemplified by mice and rats. Mice are art-recognized model mammalian systems for studying the effects of the isolated MDCs after introduction into the animals. The results obtained in mice and rats can be used to reasonably predict

effects and results of the methods employed in other mammals, including humans. A declaration provided by Dr. Cannon states that results of the studies using MDCs in a mouse model are reasonably predictive of results that would be obtained in other mammals, including humans. (Cannon declaration, ¶ 5).

Without evidence provided by the Examiner, there is no reason not to believe that practice of the presently claimed method of plating and culturing muscle cells obtained from a muscle specimen of a mammal would not yield a population of MDCs according to the teaching and specific guidance as set forth in the applicants' disclosure. The methods of making and using applicants' MDCs are clearly described and can be routinely practiced without undue experimentation by a person of skill in the pertinent art.

Moreover, should phenotypic marker analysis be performed on the MDCs isolated by the presently claimed method, such analysis can be used to further characterize the MDCs obtained by the claimed isolation method. One having skill in the art can determine, as desired, surface markers expressed by MDCs obtained by the described method using routine skill. (See, e.g., page 30, Table 1; page 40, lines 27-31 to page 41, lines 1-12; and pages 46-47, line 25 of the instant specification). Such marker analysis can be employed to further identify the MDCs already obtained by practicing the MDC isolation method of the present invention. It is recognized by those having skill in the relevant art that certain of the phenotypic markers may be shared among many mammalian species, while others may have species counterparts that perform similar function. This knowledge is routine and does not involve undue experimentation to practice the invention as presently claimed.

The Examiner has further remarked that the specification only provides sufficient guidance for making murine or rat pp6 cells. (03/11/2003 Office Action, p. 11). The Examiner opines that "[i]t would take one skilled in the art an undue amount of experimentation to reasonably correlate from the working examples to any claimed therapeutic method in any mammal other than mice or rats ... because of the lack of

guidance for making other types of mammalian MDCs". Applicants respectfully disagree with this reasoning.

In the specification, applicants have described a method of isolating MDCs, which can be used in the described methods of tissue bulking, augmentation, and treatment. With such guidance and teaching, one having skill in the pertinent art can subject a suspension of muscle cells from a mammal to the described MDC plating and isolation method with no undue or excessive experimentation. If human cells, e.g., a human skeletal muscle sample, are used, the MDCs isolated by the method can be used in the described methods of augmenting or bulking tissue. As the declaration of Dr. Tracy Cannon indicates, MDCs can be routinely derived from human muscle cells and can be used in the claimed methods of bulking, augmenting and treating tissue weakness and dysfunction. (Cannon declaration, ¶¶ 4 and 7).

Applicants have demonstrated the efficacy of using MDCs in reputable animal models and have taught and evidenced through examples that MDC obtained from skeletal muscle are fully capable of surviving and developing in smooth muscle tissue following introduction or transplantation into animals in an art-recognized animal model system. The MDC exhibited long-term survivability and assimilated as muscle tissue cells for two weeks or longer post injection. Thus, applicants submit that one skilled in the art would reasonably extrapolate the use of applicants' MDC in augmenting or bulking smooth muscle tissue for the types of treatment applications that are described in the instant specification, and that such applications involve routine, and not undue, experimentation. (See, also, Cannon declaration, ¶¶ 5, 6 and 9).

The Examiner cites publications related to his opinion that there is "unpredictability of muscle-derived cells differentiating into a specific muscle tissue". (03/11/2003 Office Action, p. 12). Applicants assert that the cells described in these articles are distinct from the presently claimed MDCs and do not possess the plasticity in development following introduction into a site as do the MDCs according to the present invention. In addition, in the enclosed declaration, Dr. Cannon has indicated

that the claimed MDCs can differentiate into cells of the appropriate tissue types following injection, based upon her knowledge and experience in the field.

Applicants again refer the Examiner to the two the abstracts, which are cumulative to the originally filed disclosure, provided with the 11/21/2002 response as Exhibit 13 (H. Oshima et al., 2002, "Long-term survival of novel muscle-derived stem cells after transplantation into myocardium", 10th International Congress on Neuromuscular Disease, July 7-12, 2002, Vancouver, Canada), and Exhibit 14 (T. Payne et al., 2002, "Novel muscle-derived stem cells deliver dystrophin into a dystrophin-deficient murine heart", 10th International Congress on Neuromuscular Disease, July 7-12, 2002, Vancouver, Canada) reporting studies that were carried out based solely on the teachings of the instant application and performed in the laboratories of the named inventors. The abstracts support the teachings of applicants' disclosure (e.g., Example 7, page 39) and demonstrate that skeletal muscle derived MDC exhibit long term survival (e.g., for 8 weeks and more) and associate with heart muscle (non-skeletal muscle) components following transplantation into heart muscle (myocardium).

Another abstract submitted as Exhibit 15 with applicants' 11/21/2002 response (i.e., B. Cao et al., 2002, "Muscle stem cells differentiate into hematopoietic lineage but retain myogenic potential", 10th International Congress on Neuromuscular Disease, July 7-12, 2002, Vancouver, Canada) reports that MDCs disseminate and restore dystrophin in the gastrocnemius muscles of injected irradiated recipient adult mdx mice, and that these cells possess long-term repopulating capacity and plasticity in being able to differentiate into hematopoietic lineage cells. These ongoing studies based on the teachings of applicants' disclosure support both the actual practice of the presently claimed invention and the benefits afforded by the disclosed MDC-based treatments and therapies.

It is thus respectfully submitted that all of the presently pending claims satisfy the requirements of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the §112, first paragraph rejection are respectfully requested.

Double Patenting

Claims 1, 3 and 84 and claims 100, 101 and 106 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 76-80 of co-pending application U.S. Serial No. 09/302,896. According to the Examiner, the conflicting claims are not identical, but are considered to be obvious variants of one another.

The applicants will address this rejection by the filing of a terminal disclaimer upon indication of allowability of subject matter in the instant application.

The claims fulfill the requirements of 35 U.S.C. § 102

Claims 106 stands rejected under 35 U.S.C. § 102 (e) as being anticipated by Anderson (U.S. Patent No. 6,001,654), ("the '654 patent"). The Examiner remarks that Anderson teaches isolated smooth muscle progenitor cells (Col. 13, lines 23-26 and Col. 16, lines 53-67).

It is well established that to anticipate under §102, each and every limitation of a claimed invention must be disclosed in a single reference. *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 57 USPQ2d 1057 (Fed. Cir. 2000; *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001).

Applicants submit that claim 106, re-presented as claim 113 herein, is patentably distinct from the disclosure of the '654 patent. The cited passages do not remotely teach the instant muscle derived progenitor cells (MDCs) described in the instant application. The MDCs as newly described by the applicants are obtained by a plating method that is neither taught nor contemplated by the '654 patent. Unlike the presently claimed invention, the '654 patent is concerned with neural crest stem cells isolated from the neural tubes of embryos and grown and cultured in the presence of fibronectin

in a defined medium. The cells are contacted with one or more growth factors to stimulate their differentiation into neuronal or smooth muscle cell populations. (See, Abstract and Examples 1-6, Cols. 20-29 of the '654 patent).

Because the '654 patent to Anderson et al. fails to disclose each and every element of applicant's claimed invention, arranged as in the claim, this reference does not anticipate the present claims. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claim 106 also stands rejected under 35 U.S.C. § 102(b) as being anticipated by Huard et al. (IDS, 1994, Muscle & Nerve, pp. 224-234). According to the Examiner, "Huard teaches human myoblasts obtained from a postmortem biopsy of a 13 month-old boy (p. 225)".

It is well established that to anticipate under §102, each and every limitation of a claimed invention must be disclosed in a single reference. *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 57 USPQ2d 1057 (Fed. Cir. 2000; *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001).

Applicants submit that claim 106, (new claim 113 herein), is patentably distinct from the cited Huard et al. publication. This publication does not teach or suggest applicants' claimed MDCs, which are obtained by a method that is not taught or disclosed in the 1994 Huard et al. publication. Huard et al. teaches that the human myoblasts as described in the paper were obtained by a conventional procedure involving direct cell cloning and subsequent inoculation of cells into petri dishes in defined growth medium in which the cells were incubated for 14 days without a medium change. This procedure is distinctly different from the method of MDC isolation as taught and claimed by the applicants.

Accordingly, because each and every element of applicants' invention is not found in the cited Huard et al. publication, this reference fails to anticipate applicants'

presently claimed subject matter. Reconsideration and withdrawal of this rejection are thus respectfully requested.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance and that the claims as presented are in condition for allowance or in better form for appeal. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this amendment and response, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. 08-0219.

If the Examiner is of the opinion that further discussion of the application would be helpful, the Examiner is hereby respectfully requested to telephone the applicants' undersigned representative at (212) 937-7315 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

HALE AND DORR LLP

Date: July 28, 2003

By: Leslie Serunian
Leslie A. Serunian
Registration No. 35,353

Correspondence Address:
HALE AND DORR LLP
300 Park Avenue
New York, New York 10022
Telephone: (212) 937-7200
Facsimile: (212) 937-7300
Direct Tel.: (212) 937-7315